REMARKS

Claims 26-37 are pending in the application, with claims 26-30 being independent. Claims 1-25 have been cancelled without prejudice or disclaimer. Support for new claims 26-38 may be found in previously presented claims 13-25. Further support for claims 31 and 32 may be found in the specification at page 2, lines 7-20. No new matter has been introduced.

Claims 28 and 29 have been written to refer to a figure in the specification. Applicants respectfully submit that these claims were written in accordance with M.P.E.P. 2173.05(s). Claims that are written to incorporate by reference a specific figure or table are not improper and are not considered indefinite. Applicants respectfully submit that M.P.E.P. 2173.05(s) provides full support for drafting claims to incorporate by reference to a specific figure or table, where "there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim." Accordingly, Applicants respectfully submit that these claims present a situation where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim.

The Examiner objected to previously presented claims 24 and 25 as being substantial duplicates of claim 1, indicating that the objection could be overcome by deleting claim 25. The subject matter of claim 25 has not been included in the newly presented claims. Applicants, however, expressly reserve the right to present the cancelled subject matter in a claim in a subsequently filed application.

Summary of Claim Rejections

Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 20, 21, 22, 23, 24, and 25 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Smith et al (WO 98/57634). Claims 20, 21, 22, 23, 24, and 25 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Andersen et al. (WO 97400177) in further view of Patani. Claims 20-21 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 10 of copending Application No. 10/030877 (WO 00/64893). Claims 20-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 10 and 14 of copending Application No. 10/048,123 (WO 00/64896) and over claims 10 and 14 of copending Application No. 10/703,887 (WO 00/64892). Claims 22-23 were provisionally

rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 12 of copending Application No. 10/030877, (WO 0063206). Claims 20-23 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12 and 16 of copending Application No. 10/082,879 (US2002137940) and over claims 12 and 16 of copending Application No. 10/321,055 (US2003/0120078 A1). Applicants respectfully traverse each of these rejections.

Arguments

Claims 13-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that the specification discloses that instant compounds were made by the methods described in EP0306228 and WO9405659 (OA-page 2, last paragraph) and that there is no description as to how the applicant produced and isolated the particular dihydrate being claimed (OA-page 4, first paragraph). Applicants respectfully submit that the specification, at page 1, lines 5-11 actually states that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione and certain salts thereof (and procedures for the preparation thereof) are disclosed in the cited references. The subject specification does not state that the compound of the present invention, the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione *hydrochloride dihydrate*, characterized by the defined IR spectrum and XRPD pattern and data, is made by any method of the cited references. It can be noted, however, that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione is a starting material used for the preparation of the *hydrochloride dihydrate* compound of the present invention. The Examiner's attention is directed to page 7 of the specification, where Examples 1-3 provide experimental details for 3 ways to produce the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, *hydrochloride dihydrate* of the present invention.

The Examiner also contends that there is a lack of description as to which pharmaceutical carriers are able to maintain the compound in the claimed hydrate form (OA-page 3, second paragraph) and that there is a lack of disclosure as to how the claimed polymorphic form can be maintained and/or prevented from converting to other forms.

As an initial matter, Applicants respectfully submit that there is simply no basis or support in the subject specification or in the art for the assumptions inherent to the Examiner's contention - that the claimed polymorphic form is inherently unstable or unstable in the solid state, that some action needs to be taken to maintain and/or prevent the claimed

form from converting into other forms or that the presence of specific pharmaceutical carriers is required to maintain the claimed form. Applicants have discovered a novel crystalline form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride existing as a dihydrate, that is suitably stable for characterization by IR spectroscopy and XRPD pattern analysis. The composition and method of treatment claims of the subject application are directed to those compositions and methods of treatment that contain or use a form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, where such form, when analyzed by IR or XRPD, provides the claimed IR or XRPD data. If at any future time the claimed compound form converts into a new, distinct compound form, then such new form, composition containing such new form or method of treating diabetes using such new form would not be encompassed within the scope of the pending claims.

The Examiner contends that Applicants are not entitled to the XRPD patterns and IR spectra claimed for the pharmaceutical compositions being claimed (OA-page 3, last paragraph, page 6-7, bridging paragraph) and appears to fault the specification for not providing XRPD patterns for the claimed pharmaceutical compositions (OA-page 4, second paragraph, and page 7, third paragraph). Applicants wish to point out that the claims 20-22 (new claims 33 and 34) do not claim the pharmaceutical compositions in terms of XRPD patterns and/or IR spectra of the composition. Claims 33 and 34 incorporate XRPD pattern and IR spectral data as related to "the compound" that is present in the composition (the compound according to any one of claims 26-29) – not as related to the composition as a whole.

Applicants respectfully request clarification as to why the Examiner considers it important or even useful to provide an XRPD pattern for a pharmaceutical composition. Many conventional pharmaceutical carriers/excipients are crystalline materials and most pharmaceutical compositions are mixtures of more than one carrier/excipient. Accordingly, it appears that the Examiner may be requesting/requiring XRPD pattern data on a mixture of carrier materials, some of which may be crystalline, admixed with relatively small amounts of the crystalline 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention. (As indicated in WO98/57649, WO98/57634, WO98/57635, and/or WO98/57636 (see page 5, lines 25-32 of the subject specification), a useful formulation and dosage form for a pharmaceutical composition of this invention is a tablet containing 1mg - 12mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, thus the amount of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione in such compositions would be about

0.6% to about 4% - assuming that the typical weight of a tablet ranges from about 150mg to about 300mg.) Applicants respectfully submit that it would be doubtful that an XRPD of such a mixture would provide useful information. Clarification of the Examiner's position is respectfully requested.

The Examiner (OA-page 7, second paragraph) considers the breadth of the previously pending claims 13-25 to encompass pharmaceutical compositions, the specific polymorph and method of treating diabetes with "all polymorph and nonpolymorph forms" of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. Presumably relying on this assessment, the Examiner also contends that the specification lacks direction or guidance for placing all of the alleged products in the possession of the public (OA-page 5, first paragraph).

Applicants respectfully wish to note that the only independent claims presented for examination in the course of prosecution in this case (cancelled claims 1 and 13 and pending claims 26-30) have been "compound" claims directed to a form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate that is characterized by the defined XRPD pattern and/or IR spectrum data. All other composition and method of treatment claims depend from, and thereby include all of the limitations of the independent compound claims. (37 C.F.R. §1.75: Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim.) Applicants cannot ascertain any basis for the Examiner to construe any claim in this case to encompass "all polymorph and nonpolymorph forms" of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. Accordingly, Applicants respectfully submit that the subject specification provides adequate direction and guidance for preparing, formulating and using the form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention. Review and clarification of the Examiner's determination of the breadth of the pending claims is respectfully requested.

Former claim 17 was rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants have not used this term in the pending set of claims, however, Applicants expressly reserved the right to prosecute claims to an isolated 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate in a subsequently filed continuation application.

Claims 20, 21, 22, 23, 24, and 25 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Smith et al and rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Andersen et al. (WO 97/400177, see CA 128:3688) in further view of Patani.

Applicants note that Patani has not been made of record in this case nor has a copy of this reference been provided by the Examiner. Accordingly, Applicants can address the rejection only in terms of the disclosure of the cited Anderson reference. Claims 21-23 were also rejected for obvious-type double patenting. Applicants, again, respectfully traverse each of these rejections.

As an initial matter, Applicants respectfully wish to note that previously presented claims 20, 21, 22, 23, 24, and 25 are composition claims that are dependent upon previously presented compound claims 13-16 (pending claims 26-29). Applicants also wish to note that the Examiner has not made any novelty or obviousness rejections relating to the compound form defined in claims 13-16 (pending claims 26-29). Accordingly, Applicants respectfully submit that if the claimed compound form is considered novel and unobvious, the corresponding claims to methods of making, methods of using or compositions containing such a novel and unobvious compound form, must likewise be considered novel and unobvious. *In re Ochiai*, 37 USPQ2d 1127(Fed. Cir. 1995)

It is well established that "[a]nticipation requires the presence in a single prior art reference disclosure of every element of the claimed invention." *Great Northern Corporation v. Davis Core & Pad Co., Inc.*, 228 U.S.P.Q. 356, 358 (Fed. Cir. 1986). It is similarly well established that one of the basic criteria for establishing a *prima facie* case of obviousness requires that the cited references disclose all of the claim limitations. (M.P.E.P 2143) Applicants respectfully submit that none of the cited references nor any of the claims of the cited patents disclose or claim any composition or method of treatment that contains or uses the specific form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate that is characterized by the IR spectrum and/or XRPD pattern data defined in the pending claims. Accordingly, none of the cited references or patent applications renders the presently claimed compositions unpatentable.

In support of the rejection under 35 U.S.C. §103(a), the Examiner asserted that it would have been obvious to synthesize bioisosteres of the thiazolidinedione described in Anderson to obtain 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. Applicants respectfully submit that the Examiner's assertion is not supported by the references of record in this case. As the Examiner noted on page 3 of the office action, 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione was disclosed in EP 0306228, which published in 1989. It would seem impossible for the thiazolidinedione of Anderson, which appears to have been first disclosed in 1997, to have been used as the bio-isosteric model for the thiazolidinedione, 5-[4-[2-(N-methyl-N-(2-

pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, which was disclosed nearly 8 years earlier.

In support of the provisional double patenting rejections, the Examiner contends that the method of treating diabetes mellitus with the claimed compound and a pharmaceutical composition containing this compound are identical to the pharmaceutical composition and method of treating diabetes mellitus of the cited applications.

The rejected claims 21-23 are directed to pharmaceutical compositions comprising the compound form of this invention and to methods of treatment of diabetes comprising administering the compound form of this invention. The scope of these claims requires the presence of the compound, 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, in a crystalline from that can be characterized by the defined IR spectrum and/or XRPD pattern data. These claims are not directed to compositions that contain or methods that comprise administering any other distinct crystalline form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, any other form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, or any other form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. The Examiner has provided no basis, no theory, nor any mechanism by which the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate form of this invention converts to any one of the crystal forms of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione maleate in the cited applications. To achieve this feat, there must be an exchange of counter-ion (chloride for maleate) which would constitute a chemical transformation that would not be possible in the solid state. Applicants respectfully submit that hydrochloride dihydrate form of this invention is distinct from each and every one of the maleate forms in the cited applications. That the materials possess different counter-ions (i.e., are chemically distinct salts) and possess different states of hydration should be sufficient to establish the fact that the materials are different. However, if the Examiner remains unconvinced, she is invited to compare the XRPD patterns for each of the maleate forms and the hydrochloride dihydrate form of this invention and observe that each of the XRPD patterns are unique, and accordingly, conclude that each of the maleate forms and the hydrochloride dihydrate form of this invention possess unique crystal forms.

In support of the provisional double patenting rejections, the Examiner also asserted that the cited applications allegedly anticipate the presently claimed compositions and methods of treatment, since at physiological conditions, the maleate compound of the cited

applications is identical to the presently claimed compound form. Applicants wish to point out that the physiological active state of the compound form of this invention (formed after administering the compound or composition of this invention) would most likely be a dissolved state. In a dissolved state, the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (if it remained associated with a chloride counter-ion) would likely be associated with more than two water molecules. Moreover, in a dissolved state, 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione could not be characterized by XRPD – XRPD is a solid state technique. As discussed above, the scope of the pending composition and method of treatment claims requires the presence of the compound, 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, in a crystalline from that can be characterized by the defined IR spectrum and/or XRPD pattern data.

Applicants believe that they have addressed each of the Examiner's concerns and met each of the objections. If the Examiner has any remaining objections or concerns, the Examiner is respectfully requested to contact Applicants' undersigned attorney to resolve such issues and advance the case to issue.

This Amendment is being filed together with a Petition for Extension of Time. In the event that these papers get separated, this constitutes a Petition for Extension of Time for the minimum period required to effect timely filing of this Amendment, together with an authorization to charge any fees under 37 C.F.R. §1.16 or §1.17 which may be required by this paper to Deposit Account No. 19-2570.

Respectfully submitted,

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